Bronchial Thermoplasty

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers bronchial thermoplasty experimental and investigational for the treatment of asthma and other indications (e.g., chronic obstructive pulmonary disease) because its effectiveness has not been established.

See also CPB 0670 - Xolair (Omalizumab) (/600_699/0670.html).

Background

Asthma is one of the most common chronic diseases in the United States, and its prevalence has been increasing since 1980. In 2000, asthma was responsible for 4,487 deaths, about 0.5 million hospitalizations, 1.8 million visits to the emergency room, and 10.4 million visits to the physician office among individuals of all ages. The Behavioral Risk Factor Surveillance System (BRFSS) collects data each year from the 50 states, the District of Columbia, and 3 United States territories to provide prevalence data for state and local health department asthma programs. Findings from BRFSS indicated that approximately 7.2% of adults in the United States have current asthma (CDC, 2003). According to the National Heart, Lung and Blood Institute's (2002) global strategy for asthma management and prevention, the preferred therapy for patients with moderate persistent asthma is regular treatment with a combination of inhaled...
corticosteroids and a long-acting inhaled beta 2-agonist twice-daily. For patients with severe persistent asthma, the primary therapy includes inhaled corticosteroid at higher doses plus a long-acting inhaled beta 2-agonist twice-daily.

Bronchial thermoplasty (BT) is a bronchoscopic procedure that employs radiofrequency ablation to reduce the mass of airway smooth muscle (ASM), thus attenuating bronchoconstriction. It is being studied as a minimally invasive method to improve asthma control. Bronchial thermoplasty has been suggested as a treatment for severe asthma in individuals ages 18 or older whose asthma is not well controlled with standard medical therapy (eg, inhaled corticosteroids and long-acting beta-agonists). This treatment was designed to reduce, debulk or partially eliminate excess smooth muscle tissue in the distal airways in order to decrease the number of severe asthma attacks. One example of a US Food and Drug Administration (FDA) approved bronchial thermoplasty system is the Alair bronchial thermoplasty system.

Bronchial thermoplasty is performed on an outpatient basis with conscious sedation (i.e., no general anesthesia is needed), and it usually takes approximately one hour to complete. During the outpatient procedure, a flexible bronchoscope is inserted into the lungs via the individual’s mouth or nose. The thermoplasty catheter is then introduced through a channel within the bronchoscope. Once in place, the catheter tip expands to allow four electrodes to make contact with the airway wall. Using a radiofrequency controller, the physician delivers controlled thermal energy to heat smooth muscle in the airway wall to approximately 150 degrees Fahrenheit (enough to thin smooth muscle tissue mass without causing tissue damage or scarring). General anesthesia may be used, but individuals typically receive an intravenous sedative and remain conscious during the procedure, which takes less than one hour. Three sessions are usually required at a minimum of three week intervals to treat all accessible airways in both lungs.

Bronchial thermoplasty is not intended to be performed on individuals with asthma who have a known sensitivity to atropine, benzodiazepines, lidocaine or for those with a pacemaker, implantable cardioverter defibrillator or other implantable electronic devices.

There are 2 assumptions that underlie the development of this procedure: (i) ASM is a vestigial tissue; and (ii) treatment directed at ASM alone will provide sustained symptomatic and physiological improvement in patients with asthma.

Mitzner (2006) discussed the potential of BT in preventing serious consequences resulting from asthma. The most important factor in minimizing an asthmatic attack is limiting the degree of smooth muscle shortening. The premise that ASM can be either inactivated or obliterated without
any long-term alteration of other lung tissues, and that airway function will remain normal, albeit with reduced bronchial constriction, has been demonstrated in dogs, a subset of normal subjects, as well as mild asthmatics. Bronchial thermoplasty may thus develop into a useful clinical procedure to effectively impair the ability for ASM to reach the levels of pathological narrowing that characterizes an asthma attack. It may also enable more successful treatment of asthma patients who are unresponsive to more conventional therapies. Whether this will remain stable for the lifetime of the patient still remains to be determined, but at the present time, there are no indications that the smooth muscle contractility will return. The authors concluded that this preliminary experience showing that BT could be safely performed in patients with asthma has led to an ongoing clinical trial at a number of sites in Europe and North America designed to examine the effectiveness of this procedure in subjects with moderately severe asthma.

In a prospective study, Miller et al (2005) evaluated the feasibility and safety of BT in the human airway, and determined if the reduction in ASM observed in animal studies could be replicated. A total of 9 patients scheduled to undergo lung resection for suspected or proven lung cancer received BT during routine preoperative bronchoscopy up to 3 weeks prior to pre-scheduled lung resection. Treatment was limited to areas of the segmental bronchi within the lobe that was to be removed. Treated airways were inspected via bronchoscopy at the time of thoracotomy, and were examined histologically following surgical resection. There were no adverse clinical effects of the procedure, including no new symptoms and no unscheduled visits for medical care. Treated sites exhibited slight redness and edema of the mucosa within 2 weeks of treatment, and appeared normal at later time points. There was narrowing (visually estimated at 25 to 50%) in four airways in 2 subjects examined at 5 days and 13 days after treatment, with excess mucus in two of these airways. There was no bronchoscopic evidence of scarring in any of the airways examined. Histological examination showed a reduction in ASM, and the extent of the treatment effect was confined to the airway wall and the immediate peri-bronchial region. The authors concluded that BT to the human airway appears to be well-tolerated, and treatment resulted in significant reduction of smooth muscle mass in the airways. They noted that BT may provide therapeutic benefit in disease states such as asthma.

Cox et al (2006) examined the safety and impact on lung function and airway responsiveness of BT over 2 years in 16 subjects with mild-to-moderate asthma. Baseline and 12-week post-treatment measurements included spirometry, methacholine challenge, daily diary recordings of peak flow, symptoms, and medication usage. Subjects completed follow-up evaluations at 12 weeks, 1 year, and 2 years. The procedure was well-tolerated; side effects were transient and typical of what is commonly observed after bronchoscopy. All subjects reported improvement in airway responsiveness. The mean PC(20) increased by 2.37 +/- 1.72 (p < 0.001), 2.77 +/- 1.53 (p = 0.007), and 2.64 +/- 1.52 doublings (p < 0.001), at 12 weeks, 1 year, and 2 years post-procedure, respectively. Data from daily diaries collected for 12 weeks indicated significant
improvements over baseline in symptom-free days ($p = 0.015$), morning peak flow ($p = 0.01$), and evening peak flow ($p < 0.007$). Spirometry measurements remained stable throughout the study period. The authors concluded that BT is well-tolerated in patients with asthma and results in decreased airway hyper-responsiveness that persists for at least 2 years. Limitations of this case series includes its small size, lack of comparison group, and limited duration of followup. In an editorial that accompanied the afore-mentioned article, Bel (2006) noted that "whether bronchial thermoplasty will earn a place in the treatment of asthma remains to be determined. However, this study shows the potential for a completely new approach of treating asthma and stimulates the development of new hypotheses".

Cox and colleagues (2007) examined the effect of BT on the control of moderate or severe persistent asthma. These researchers randomly assigned 112 subjects who had been treated with inhaled corticosteroids and long-acting beta 2-adrenergic agonists (LABA) and in whom asthma control was impaired when the LABA were withdrawn to either BT or a control group. The primary outcome was the frequency of mild exacerbations, calculated during 3 scheduled 2-week periods of abstinence from LABA at 3, 6, and 12 months. Airflow, airway responsiveness, asthma symptoms, the number of symptom-free days, use of rescue medication, and scores on the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) were also assessed. The mean rate of mild exacerbations, as compared with baseline, was reduced in the BT group but was unchanged in the control group (change in frequency per subject per week, -0.16 +/- 0.37 versus 0.04 +/- 0.29; $p = 0.005$). At 12 months, there were significantly greater improvements in the BT group than in the control group in the morning peak expiratory flow (39.3 +/- 48.7 versus 8.5 +/- 44.2 L/min), scores on the AQLQ (1.3 +/- 1.0 versus 0.6 +/- 1.1) and ACQ (reduction, 1.2 +/- 1.0 versus 0.5 +/- 1.0), the percentage of symptom-free days (40.6 +/- 39.7 versus 17.0 +/- 37.9), and symptom scores (reduction, 1.9 +/- 2.1 versus 0.7 +/- 2.5) while fewer puffs of rescue medication were required. Values for airway responsiveness and forced expiratory volume in 1 second did not differ significantly between the 2 groups. Adverse events immediately after treatment were more common in the BT group than in the control group but were similar during the period from 6 weeks to 12 months after treatment. The authors concluded that BT in subjects with moderate or severe asthma results in an improvement in asthma control. Limitations of the study included the lack of blinding, raising the criticism that the improvement in symptoms among people getting BT was purely due to a placebo effect after undergoing an invasive procedure. In addition, the primary study outcomes of bronchial thermoplasty occurred during a period of withdrawal of LABA per study protocol, which does not reflect how asthma is managed in standard clinical practice. The small increment in improvement quality of life with BT compared to the control group was of questionable clinical significance. The rate of severe adverse reactions where higher (3 percent) in the BT group compared to the control group (1 percent). The BT group also had more hospitalizations for respiratory causes (9) than the control group (5). In an editorial that
accompanied the afore-mentioned article, Solway and Irvin (2007) stated that "[b]ronchial thermoplasty represents a novel approach to targeting airway smooth muscle, but it ablates airway myocytes only in bronchi 3 mm or larger in diameter, which can be treated directly. For this reason, and because of the considerable effort involved (three separate bronchoscopic procedures, each with a small but significant risk of complications), notable adverse effects (in the short term, at least), and likely expense, bronchial thermoplasty will probably need further refinement if it is to emerge as a widely applicable, practical treatment for moderate or severe asthma. Nonetheless, the results reported by Cox and colleagues suggest that we should now contemplate other approaches to targeting airway smooth muscle that might prove to be less invasive, more practical, and more amenable to application throughout the airways".

In a subsequent publication (Thomson et al, 2011a), the investigators continued to follow the BT group for a total of five years and the control group for a total of three years. Patients enrolled in the Asthma Intervention Research (AIR) Trial were on inhaled corticosteroids greater than or equal to 200 μg beclomethasone or equivalent plus long-acting-beta2-agonists and demonstrated worsening of asthma on long-acting-β2-agonist withdrawal. Following initial evaluation at 1 year, subjects were invited to participate in a 4-year safety study. Adverse events and spirometry data were used to assess long-term safety out to 5 years post-BT. A total of 45 of 52 treated and 24 of 49 control group subjects participated in long-term follow-up of 5 years and 3 years, respectively. The rate of respiratory adverse events (AEs) per subject was stable in years 2 to 5 following BT (1.2, 1.3, 1.2, and 1.1, respectively). There was no increase in hospitalizations or emergency room visits for respiratory symptoms in years 2, 3, 4, and 5 compared to year 1. The forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) values showed no deterioration over the 5-year period in the BT group. Similar results were obtained for the control group. The authors concluded that absence of clinical complications (based on AE reporting) and the maintenance of stable lung function (no deterioration of forced vital capacity and FEV(1) over a 5-year period post-BT in this group of patients with moderate-to-severe asthma support the long-term safety of the procedure out to 5 years. However, it is interesting to note that similar results were obtained in the control group. During the three years of long-term follow-up with data comparing the two groups there were no differences in the clinically relevant outcomes: hospitalizations, emergency room visits, and oral steroids to treat respiratory exacerbations. Although the outcomes of this study suggest that the benefits of BT persist and no unexpected respiratory pathologies develop, the sample size was small, so considerable uncertainty remains.

Pavord et al (2007) examined the safety and effectiveness of BT in patients with symptomatic, severe asthma. Adults who were symptomatic despite treatment with fluticasone or equivalent at more than 750 mug/day and other medications, which could include 30 mg or less of oral prednisolone/day, were randomized to BT or to a control group. After treatment, subjects entered
a 16-week steroid stable phase (weeks 6 to 22), a 14-week steroid wean phase (weeks 22 to 36), and a 16-week reduced steroid phase (weeks 36 to 52). Bronchial thermoplasty resulted in a transient worsening of asthma symptoms. Seven hospitalizations for respiratory symptoms occurred in 4 of 15 patients who received BT during the treatment period. Five hospitalizations were within 3 days of treatment. Two subjects had segmental collapse involving the most recently treated lobe; 1 required bronchoscopy and aspiration of a mucus plug. There were no hospitalizations during this period in the 17 control subjects. The rate of hospitalizations was similar in both groups in the post-treatment period. At 22 weeks, patients who received BT had significant improvements versus control subjects in rescue medication use (-26.6 +/- 40.1 versus -1.5 +/- 11.7 puffs /7 day, p < 0.05), pre-bronchodilator forced expiratory volume in 1 second [FEV(1)] % predicted (14.9 +/- 17.4 versus -0.94 +/- 22.3 %, p = 0.04), and Asthma Control Questionnaire scores (-1.04 +/- 1.03 versus -0.13 +/- 1.00, p = 0.02). Improvements in rescue medication use and ACQ scores remained significantly different from those of controls at 52 weeks. The authors concluded that BT is associated with an excess of hospitalizations and a short-term increase in asthma-related morbidity. However, there is preliminary evidence of long-lasting improvement in asthma control. However, the results of this study may be biased because it was a small trial with large imbalances in important participant characteristics at baseline. The study is also limited because of lack of blinding.

Wechsler (2008) noted that BT holds promise in the management of patients with asthma. Herth (2008) stated that a short-term increase in morbidity due to bronchoscopy is to be expected with BT. The author noted that further trials are needed to investigate the value of this method, particularly with regard to long-term effects. Jesudason (2009) stated that BT is a new treatment for refractory asthma. However, the mechanism of its effects is unclear.

In a review on BT for the treatment of asthma, Martin and Pavord (2009) concluded that applying thermal energy to the airway in the form of BT results in the selective destruction of ASM; this is replaced by fibrous connective tissue. In early animal and human studies, this was associated with a reduction in objective measurements of asthma control, such as airway hyper-responsiveness (AHR). However, in the 2 published randomized controlled trials (RCTs) on this technique, there has been a failure to show improvements in AHR, although there have been significant improvements in more subjective measurements of asthma control. Neither trial was blinded, and concern remains about a significant placebo effect of the treatment. The AIR2 Trial, which is randomized and blinded with a sham treatment arm, has been designed to try to address these issues in more detail.

In randomized sham-controlled clinical study of BT in patients with refractory asthma (AIR2 study), Castro et al (2010) reported a significant improvement in Asthma Quality of Life scores in patients treated with bronchial thermoplasty. However, subjects assigned to a sham procedure
also experienced a significant improvement from baseline, such that the difference between subjects treated with BT versus subjects treated with a sham procedure was of questionable clinical significance. In this study funded by AsthmaX, Castro et al (2010) evaluated the effectiveness and safety of BT versus sham procedure in subjects with severe asthma who remain symptomatic despite treatment with high-dose inhaled corticosteroids and long-acting beta 2-agonists. In this study, 288 adult subjects were randomized to BT or sham control underwent three bronchoscopy procedures. Primary outcome was the difference in a Asthma Quality of Life Questionnaire (AQLQ) scores from baseline to average of 6, 9, and 12 months (integrated AQLQ). The AQLQ is a 7-point Likert scale, where a 0.5 change in score is considered the minimally important difference. Subjects assigned to BT had an average 1.35 +/- 1.10 improvement over baseline in integrated AQLQ score. However, subjects assigned to a sham procedure had an average 1.16 +/- 1.23 improvement over baseline. The 0.19 point difference between the BT and sham control group fell short of the cutoff of 0.5 points for a minimally important difference in the AQLQ. There were more respiratory adverse events in the BT group during the initial treatment period including an excess of hospitalizations. After the initial treatment period, there was a reduction in ER visits, but not in hospitalizations for the BT group compared to the sham group.

An editorial that accompanied the afore-mentioned study by Castro et al, Bel (2010) noted that "[t]he trial demonstrated that 6 to 12 months after the procedure, bronchial thermoplasty had a small, but significantly greater mean positive effect on the asthma-related quality of life score than did the sham procedure. The mean difference in score was 0.19, which was statistically significant but substantially smaller than the minimum clinically important difference of 0.5. Remarkably, not one of the secondary outcomes showed a difference between bronchial thermoplasty and sham procedure. Additional outcomes that were collected to assess safety showed that during the post-treatment period there were less severe exacerbations and emergency room visits in the bronchial thermoplasty group compared with the sham control group, but over the entire study period there was no difference in outcomes between the groups". Furthermore, Bel (2010) stated that "[t]he overall net effect of bronchial thermoplasty in the AIR2 trial is somewhat disappointing. Although airway hyperresponsiveness as a most relevant outcome of bronchial thermoplasty is difficult to measure in patients with severe asthma, one would have hoped to see at least an effect on asthma control, use of rescue medication, or pre/post-bronchodilator FEV1. This was not the case. Instead, the authors observed a reduction in the rate of severe exacerbations and emergency department visits in the post-treatment period. This safety outcome was completely unexpected and was not considered in the rationale and hypothesis of the study. How can this be explained in the absence of any improvement in asthma control? Does it suggest that bronchial thermoplasty has more effects than just inactivating the airway smooth muscle? Does it suggest that the procedure might alter the inflammatory or neurogenic responses to viral infection or other triggers of asthma
exacerbations?" On the question of whether BT should be offered to patients with severe asthma, Bel (2010) stated that "[f]or patients with uncontrolled asthma who have not been submitted to a rigorous treatment protocol, the answer is no. For the remaining patients, the AIR2 results might offer some hope. Bronchial thermoplasty appears to have a benefit on the quality of life and severe exacerbations. Importantly, severe asthma has many phenotypes, and at present we have no clue which phenotype will benefit the most. It is inevitable that phenotypic targeting will be essential for this invasive procedure. Moreover, we need to know how durable the benefit will be to ensure that the benefits outweigh the risks and burden of the procedure. Therefore, long-term clinical and morphological research in various severe-asthma phenotypes is still needed to obtain the required information for clinical decisions".

Commenting on the AIR2 trial, Wahidi & Kraft (2012) noted that patients treated with bronchial thermoplasty had a slight 0.19 point improvement in AQLQ scores (1.35 vs. 1.16 with sham procedure), falling well short of the cutoff of 0.5 points for a "clinically meaningful" improvement in the AQLQ over the sham group. Moreover, both the sham and bronchial thermoplasty groups experienced a clinically meaningful improvement in AQLQ, again raising the question of whether it was the experience of undergoing an invasive procedure that led to the patient-perceived benefits. The authors noted that no differences were noted between the groups in FEV1, peak flow, or rescue medication use. However, the patients treated with bronchial thermoplasty had significantly fewer emergency room visits, severe exacerbations, and days missed from school or work. These benefits persisted on follow-up studies at 2 years, although the sham group was not followed for comparison. The authors noted that the AIR2 trial was also criticized because of its approach to patient selection: the average FEV1 was ~78% predicted, although less than 60% is considered representative of severe asthma by the National Asthma Education and Prevention Program. Patients with more severe asthma (low FEV1, greater than 2 exacerbations or pneumonias in the previous year, or greater than 3 oral steroid bursts in the previous year) were excluded, opening questions about extrapolations of any benefits of bronchial thermoplasty to these patients.

In an editorial, Michaud and Ernst (2011) commented on the selection of quality of life as the primary endpoint of AIR2 because that endpoint can be affected by unintentional unmasking of treatment assignment. "The selection of a soft primary end point, a quality-of-life measure, is concerning because a significant proportion of patients in the intervention group accurately determined their study assignment at the time of their second bronchoscopy (thermoplasty, 0.011; control, 0.342)." They also faulted the study for failing to assess whether bronchial thermoplasty resulted in a clinically important change in medication use.
Thermoplasty is a novel experimental therapeutic option that consists of delivering radiofrequency-generated heat to the airways via a catheter inserted in the bronchial tree through a flexible bronchoscope to reduce smooth muscle quantity and contractility. The first investigations were conducted using an animal model. Subsequently, 2 RCTs designed to evaluate the safety and efficacy of BT in patients with moderate-to-severe asthma with a 1-year follow-up period showed the procedure to be safe, with mostly transient adverse affects and several clinical benefits. The authors stated that, although results from ongoing clinical trials are still awaited, BT may become an innovative therapeutic approach to asthma.

In a review, Cox (2010) noted that asthma can be provoked by a wide range of stimuli that include infectious, allergic, and environmental agents. Bronchoconstriction determines much of the short-term variability in airflow that characterizes asthma. Current treatments do not redress the excess smooth muscle mass that is present in the re-modeled airway in chronic asthma. Thus, it is intriguing to consider the potential contribution of BT as a treatment for poorly controlled asthma.

In April 2010, the Food and Drug Administration (FDA) approved the Alair Bronchial Thermoplasty System (Asthmatx Inc., Sunnyvale, CA) for the treatment of patients aged 18 and older whose severe and persistent asthma is not well-controlled with inhaled corticosteroids and long-acting beta agonist medications. The FDA based its approval on data from AIR2, a clinical trial of 297 patients with severe and persistent asthma. The trial showed a reduction of severe asthma attacks with use of the Alair system. The majority of the Panel believed that the primary effectiveness endpoints were not met during clinical study of the Alair System but they were impressed by the other evaluations of effectiveness and believed that an important clinical benefit was achieved (FDA, 2009a). The original Bayesian statistical protocol of the AIR2 trial had planned seven interim analyses (FDA, 2009b). The seven interim analyses were reduced to two, one when 225 patients reached six months, the second one when the 225 patients reached nine months, and one final analysis. The design cut point to control the Type I error in the context of the seven interim analysis in the original design was 96.4% for the primary endpoint, the integrated AQLQ. The design cut point was not changed when the investigators modified the study design. The manufacturer stated that, had they done so, it would have dropped substantially to 95.2% and the primary endpoint would have achieved statistical significance (FDA, 2009b). The FDA required a 5-year post-approval study of the device to study its long-term safety and effectiveness. Asthmatx agreed to follow many of the patients who were enrolled in the clinical trial and enroll 300 new patients at several medical centers across the United States.
According to the product labeling, possible side effects during the course of treatment may include anxiety, asthma attacks, atelectasis, chest tightness or pain, headaches, hemoptysis, nausea, and wheezing. While the Alair system is designed to reduce the number of severe asthma attacks on a long-term basis, there is a risk of immediate asthma attacks during the course of the treatment. Furthermore, the Alair system is not for use in asthma patients with a pacemaker, internal defibrillator, or other implantable electronic device. Also, those patients with known sensitivities to lidocaine, atropine, or benzodiazepines should not use the device. Alair has not been studied for success in re-treatment of the same area of the lung. Currently, patients should not be re-treated with the Alair system in the same area of the lung. In addition, asthma patients considering the Alair system should not be treated while the following conditions are present: an active respiratory infection, asthma exacerbations, coagulopathy, or if they have had changes to their corticosteroid regimen 14 days before the proposed treatment.

Castro and colleagues (2011) examine the persistence of effectiveness of BT 2 years post-treatment in subjects with severe asthma. Subjects participating in the long-term safety follow-up phase of the AIR2 Trial were evaluated by comparing the proportion of subjects who experienced exacerbations, AEs, or healthcare utilization during the first year (year 1) after BT with the proportion of subjects who experienced the same during the subsequent 12 months (year 2). Severe exacerbations, respiratory AEs, emergency department visits for respiratory symptoms, and hospitalizations for respiratory symptoms (proportion of subjects experiencing and rates of events), and stability of pre- and post-bronchodilator FEV(1), were comparable between years 1 and 2. The proportion of subjects experiencing severe exacerbations in year 2 after BT was 23.0 %, compared with 30.9 % in year 1. The authors concluded that reduction in the proportion of subjects experiencing severe exacerbations after BT is maintained for at least 2 years.

It is also interesting to note in a recent review by Thomson et al (2011b), BT is listed as one of the emerging therapeutic option for severe asthma. This is in agreement with Colice (2011) who also listed BT as an emerging therapy for asthma. Colice concluded that although more studies are needed to examine the safety and effectiveness of both pharmacological and non-pharmacological approaches including BT, there is future promise for therapeutic advances in severe, persistent asthma. Furthermore, Oliveinstein et al (2011) reviewed alternative therapeutic strategies in the management of severe asthma including macrolide antibiotics, biologic agents, modulators of signal transduction pathways and BT. The authors noted that the challenge remains to determine the appropriate phenotype for each therapeutic strategy in view of the heterogeneity of severe asthma.
Wu and associates (2011) performed a meta-analysis of the safety and effectiveness of BT in patients with moderate-to-severe persistent asthma. An electronic literature search identified 3 RCTs of BT that recruited a total of 421 patients. Outcomes of interest were the Asthma Quality of Life Questionnaire (AQLQ) score, morning peak expiratory flow (PEF), tolerability and safety. Compared with standard medications and sham-bronchial thermoplasty, BT significantly improved AQLQ scores and PEF from baseline to the end of the trials. There were more respiratory AEs and hospitalizations for adverse respiratory events with BT than with medications or sham-treatment during the treatment period, but most events resolved, on average, within 1 week. This effect of BT was not seen during the post-treatment period. The authors concluded that additional long-term RCT are needed to confirm whether BT provides benefit to patients with moderate-to-severe persistent asthma.

The National Horizon Scanning Centre (2011) has stated: "Further longer-term safety data and data on the effect of bronchial thermoplasty on long term health outcomes such as hospitalisation rates, GP consultation rates, medication use and quality of life are awaited. Research into the exact mechanism through which the device may work and in predicting which patients are most likely to respond to this treatment is required"

The Institute for Clinical Systems Improvement's practice guideline on diagnosis and management of asthma (ICSI, 2010) does not mention the use of BT.

The California Technology Assessment Forum (Tice, 2011) concluded that use of bronchial thermoplasty for the treatment of severe, refractory asthma meets CTAF TA Criterion 1 through 5 for safety, effectiveness and improvement in net health outcomes. The CTAF assessment noted that the most important trial of BT to consider is the AIR2 trial, because it was the only trial that used a sham control to blind patients and they also ensured that staff assessing patient outcomes remained blinded to patient allocation. The CTAF assessment found a slightly greater improvement in quality of life in the BT group compared to the sham group in the AIR2 trial, but it did not meet the pre-specified criteria for statistical or clinical significance. However, the CTAF panel felt that the net improvements were sufficient in this patient population with few options. The CTAF assessment concluded that there remain some concerns about the long-term sequelae of BT, as the number of patients followed out for five years and longer is relatively small, so there may be some uncommon long-term harms that have yet to be identified.

The National Institute for Health and Clinical Excellence (NICE, 2012) issued guidance on BT for severe asthma, which states that evidence on the safety of BT is adequate in the short- and medium-term, although patients may experience exacerbation of symptoms after the procedure. The guidance states that more evidence is required on the safety of the procedure in the long-term. The guidance notes that, with regard to efficacy, there is some evidence of
improvement in symptoms and quality of life but objective evidence of improved lung function is inadequate. NICE recommends, therefore, that this procedure should only be used with special arrangements for clinical governance, consent and audit or research. Specialist Advisors to NICE stated that improvement in symptoms and quality of life, and reductions in exacerbations and in the need for admission to hospital were more relevant efficacy outcomes than the results of lung function tests. The NICE Committee noted that many patients are young and it is therefore particularly important to monitor them for any possible long-term adverse effects such as development of bronchial stenosis.

In a review on the future of chronic obstructive pulmonary disease (COPD) treatment, Martinez and colleagues (2011) listed several novel non-pharmacotherapies including creation of arteriovenous fistulas, endobronchial glue, endobronchial thermal vapor, insertion of endobronchial valves, non-invasive mechanical ventilation, and transcutaneous electrical stimulation. Bronchial thermoplasty is not mentioned as a possible therapeutic option. Furthermore, the Institute for Clinical Systems Improvement's practice guideline on diagnosis and management of COPD (ICSI, 2011) does not mention the use of BT.

James and Gupta (2011) stated that even with the use of maximum pharmacological treatment, asthma still remains uncontrolled in some cases. For such cases of uncontrolled asthma, a novel therapy, BT, has shown some promising results over the past few years. Three major trials of BT showed that it does not cause any improvement in FEV1. However, BT improved the quality of life and decreased the future exacerbations and emergency hospital visits due to asthma. But the benefit observed was too small to be clinically significant. Follow-up (2 to 5 years) results of these BT trials did not show any significant long-term adverse event related to BT. However, further independent large RCTs and results of application of BT in real hospital settings are needed to define its role in asthma management.

On behalf of the British Thoracic Society, Du Rand and colleagues (2011) published a guideline for advanced diagnostic and therapeutic flexible bronchoscopy in adults. Regarding the use of BT the guideline noted that it is a possible treatment option in selected patients with severe persistent asthma already on maximal therapy, although its place in the treatment of asthma remains to be established. The authors also noted that the long-term safety and effectiveness of this procedure remain unclear. Hence treatment should be limited to a few specialized centers in carefully selected patients. They stated that longer-term follow-up of treated patients is needed.

Boulet and Laviolette (2012) stated that BT has been shown to reduce asthma exacerbations, and improve asthma control and quality of life over a 3-year period without significant complications up to a 5-year period. It could be considered as another option in the treatment of selected patients requiring oral and/or high doses of inhaled corticosteroids to control asthma. It
should, however, be performed in specialized centers in patients who understand the potential benefits and side-effects of this technique. The response to this treatment varies from one patient to another. The authors concluded that further studies are needed to better define the role of this option in the treatment of asthma.

Wahidi and Kraft (2012) stated that RCTs of BT in severe asthma have not been able to show a reduction in airway hyper-responsiveness or change in FEV(1), but have suggested an improvement in quality of life, as well as a reduction in the rate of severe exacerbations, emergency department visits, and days lost from school or work. Strict inclusion and exclusion criteria of these trials resulted in the elimination of patients with severe asthma who experienced more than 3 exacerbations per year. Therefore, the generalizability of this treatment to the broader severe asthma population still needs to be determined. The short-term adverse events consist primarily of airway inflammation and occasionally more severe events requiring hospitalization. Long-term safety data are evolving and have shown thus far clinical and functional stability up to 5 years after BT treatment. The authors concluded that additional studies on BT are needed to establish accurate phenotyping of positive responders, durability of effect, and long-term safety.

In a review on "Severe asthma: Future treatments" O'Byrne et al (2012) stated that BT may provide benefit in improving control and reducing exacerbations in selected patients. The addition of the muscarinic antagonist, tiotropium also improves airflow obstruction, but its benefit on exacerbation risk is not yet established. Other developments being evaluated in severe refractory asthma are CXCR2 antagonists in patients with a persisting neutrophilic airway inflammation, and CRTh2 antagonists, both of which are small molecule antagonists, and hMabs against IL4 and IL-13. Finally, other approaches to reduce receptor numbers, using inhaled antisense, has shown to reduce allergen-induced airway eosinophilia, and combining different antisense against different targets may become a feasible treatment option. A variety of new treatment options are being investigated to help improve overall asthma control in patients with severe refractory asthma. These include medications to optimize lung function; BT to reduce airway smooth muscle in central airways; and those which target specific inflammatory cells or receptors of inflammatory mediators.

Mathew et al (2012) stated that as the overall prevalence of asthma has escalated in the past decades, so has the population of patients with severe asthma. This condition is often difficult to manage due to the relative limitation of effective therapeutic options for the physician and the social and economic burden of the disease on the patient. Management should include an evaluation and elimination of modifiable risk factors such as smoking, allergen exposure, obesity and non-adherence, as well as therapy for co-morbidities like gastro-esophageal reflux disease and obstructive sleep apnea. Current treatment options include conventional agents such as
inhaled corticosteroids (ICSs), LABAs, leukotriene antagonists, and oral corticosteroids. Less conventional treatment options include immunotherapy with methotrexate, cyclosporine and tacrolimus, biological drugs like monoclonal antibodies, tumor necrosis factor-α blockers and oligonucleotides, phosphodiesterase inhibitors, anti-microbials and BT.

Silvestri et al (2012) noted that over the past 15 years, patients with a myriad of pulmonary conditions have been diagnosed and treated with new technologies developed for the pulmonary community. Advanced diagnostic and therapeutic procedures once performed in an operating theater under general anesthesia are now routinely performed in a bronchoscopy suite under moderate sedation with clinically meaningful improvements in outcome. With the miniaturization of scopes and instruments, improvements in optics, and creative engineers, a host of new devices has become available for clinical testing and use. A growing community of pulmonologists is doing comparative effectiveness trials that test new technologies against the current standard of care. While more research is needed, it seems reasonable to provide an overview of pulmonary procedures that are in various stages of development, testing, and practice at this time. Five areas are covered: (i) navigational bronchoscopy, (ii) endobronchial ultrasound, (iii) endoscopic lung volume reduction, (iv) BT, and (v) pleural procedure. Appropriate training for clinicians who wish to provide these services will become an area of intense scrutiny as new skills will need to be acquired to ensure patient safety and a good clinical result.

Cayetano et al (2012) noted that BT is a novel treatment modality that employs radiofrequency energy to alter the smooth muscles of the airways. This therapy represents a radical change in the treatment paradigm from daily repetitive dosing of medications to a truly long-term and potentially permanent attenuation of perhaps the most feared component of asthma -- smooth muscle-induced bronchospasm. A large, multi-centered, double-blinded, RCT employed the unprecedented (but now industry standard for bronchoscopic studies) approach of using sham bronchoscopy as a control. It demonstrated that BT is safe, improved quality of life, and decreased frequency of severe exacerbations in the treatment group compared to the control group. Although the mechanism of action of BT is not currently completely understood, it should be considered as a valid and potentially valuable option for patients who have severe persistent asthma and who remain symptomatic despite inhaled corticosteroids and long-acting beta-2 agonists. Such patients should however be carefully evaluated at centers with expertise in managing severe asthma patients and with physicians who have experience with this promising new treatment modality.
The GINA’s practice guideline on *Global Strategy for Asthma Management and Prevention* (2012) stated that “For adult patients whose asthma remains uncontrolled despite application of this therapeutic paradigm, and referral to an asthma specialty center, bronchial thermoplasty is now a possible option in some countries. In this bronchoscopic treatment, airways are treated on three occasions with a localized radiofrequency pulse. The treatment, which itself is associated with asthma exacerbations in the months post-bronchoscopy, results in a subsequent decrease in exacerbations. There are no significant effects on lung function or asthma symptoms. Extended follow-up on a small number of patients has provided some additional support for long-term safety of bronchial thermoplasty. However, longer-term follow-up of larger number of control and active patients is needed to assess effectiveness and caution should be used in selecting patients for this procedure”. The Global Initiative for Asthma (GINA) was launched in conjunction with the World Health Organization and the National Heart, Lung and Blood Institute.

A Horizon Scan prepared by the ECRI Institute for the Federal Agency for Healthcare Research and Quality (ECRI, 2012) stated that experts commenting on BT were cautiously optimistic about its potential to offer an option for some patients with severe asthma that does not respond to medical therapies. However, experts also cited the small evidence base, lack of long-term data, serious risks associated with BT, required investment in equipment and training, and relatively small number of qualified bronchoscopists as barriers to widespread diffusion.

Doeing et al (2013a) performed BT in 8 patients with severe asthma as defined by Expert Panel Report 3 (EPR-3) guidelines who were poorly controlled despite step 5 therapy. Data were available on each subject for 1 year prior to and 15 to 72 weeks following BT. The mean (+/- SEM) pre-bronchodilator FEV1 prior to BT was 51.8 +/- 8.6 % of predicted, and the mean (+/- SEM) number of hospitalizations for asthma in the year prior to BT was 2.9 +/- 1.2. No subject had an unexpected severe adverse event due to BT. Among the 8 patients with follow-up of at least 15 weeks, there was no significant decline in FEV1 (p = 0.4). The authors concluded that these findings suggested that BT may be safe for asthma patients with severe airflow obstruction and higher hospitalization rates than previously reported.

Doeing et al (2013b) stated that BT is an emerging therapy for patients with severe persistent asthma who remain poorly controlled despite standard maximal medical therapy. Thermoplasty elicits asthma control over time by applying thermal radiofrequency energy to airways to ablate underlying smooth muscle. While this therapy is suggested to eliminate such smooth muscle permanently, no human studies have examined the possibility of treatment failure. These researchers presented the case of a 62-year old female with severe, refractory asthma symptoms who underwent BT without apparent complications. However, severe symptoms including multiple clinical exacerbations persisted despite BT treatment. Repeat endobronchial
biopsy done 6 months after BT treatment demonstrated persistent smooth muscle hyperplasia in multiple airways that previously had been treated. The patient continued to have uncontrolled, refractory asthma despite multiple therapies. The authors concluded that this case is the first to describe a failure of BT to reduce or eliminate airway smooth muscle in a patient with severe persistent asthma. It suggested the potential for treatment failure in the management of these patients after BT and highlighted the need for further study of potential BT-refractory patients.

Wechsler et al (2013) evaluated the safety and effectiveness of BT in asthmatic patients 5 years after therapy. Subjects treated with BT from the Asthma Intervention Research 2 trial were evaluated annually for 5 years to assess the long-term safety of BT and the durability of its treatment effect. Outcomes assessed after BT included severe exacerbations, adverse events, health care use, spirometric data, and high-resolution computed tomographic scans. A total of 162 (85.3 %) of 190 BT-treated subjects from the Asthma Intervention Research 2 trial completed 5 years of follow-up. The proportion of subjects experiencing severe exacerbations and emergency department (ED) visits and the rates of events in each of years 1 to 5 remained low and were less than those observed in the 12 months before BT treatment (average 5-year reduction in proportions: 44 % for exacerbations and 78 % for ED visits). Respiratory AEs and respiratory-related hospitalizations remained unchanged in years 2 through 5 compared with the first year after BT. Pre-bronchodilator FEV1 values remained stable between years 1 and 5 after BT, despite a 18 % reduction in average daily inhaled corticosteroid dose. High-resolution computed tomographic scans from baseline to 5 years after BT showed no structural abnormalities that could be attributed to BT. The authors concluded that these findings demonstrated the 5-year durability of the benefits of BT with regard to both asthma control (based on maintained reduction in severe exacerbations and ED visits for respiratory symptoms) and safety. They stated that BT has become an important addition to the treatment armamentarium and should be considered for patients with severe persistent asthma who remain symptomatic despite taking inhaled corticosteroids and long-acting β2-agonists. Whether BT is a disease-modifying therapy will depend on the results of future appropriately designed clinical studies. The main drawback of this study was the lack of a sham control group beyond 1 year.

Pavord et al (2013) evaluated the long-term safety of BT for 5 years. Patients with asthma aged 18 to 65 years requiring high-dose inhaled corticosteroids (ICSs) (greater than 750 mg/day of fluticasone propionate or equivalent) and LABAs (at least 100 mg/day of salmeterol or equivalent), with or without oral prednisone (less than or equal to 30 mg/day), leukotriene modifiers, theophylline, or other asthma controller medications were enrolled in the Research in Severe Asthma (RISA) Trial. Patients had a pre-bronchodilator FEV1 of 50 % or more of predicted, demonstrated methacholine airway hyper-responsiveness, had uncontrolled symptoms despite taking maintenance medication, abstained from smoking for 1 year or greater,
and had a smoking history of less than 10 pack-years. A total of 14 patients (of the 15 who received active treatment in the RISA Trial) participated in the long-term follow-up study for 5 years. The rate of respiratory adverse events (AEs per patient per year) was 1.4, 2.4, 1.7, and 2.4, respectively, in years 2 to 5 after BT. There was a decrease in hospitalizations and emergency department visits for respiratory symptoms in each of years 1, 2, 3, 4, and 5 compared with the year before BT treatment. Measures of lung function showed no deterioration for 5 years. The authors concluded that these findings suggested that BT is safe for 5 years after BT in patients with severe refractory asthma. The major drawbacks of this study were the absence of a control group during the longer-term follow-up as well as the small sample size (n = 14).

An UpToDate review on “Alternative and experimental agents for the treatment of asthma” (Martin, 2013) states that “The Food and Drug Administration has approved marketing of Alair Bronchial Thermoplasty System for the treatment of adult patients (greater than or equal to 18 years old) with severe asthma not well-controlled with inhaled glucocorticoids and long-acting beta agonists. Due to the risk of the procedure and modest degree of improvement, additional data are needed regarding long-term effects and morphologic changes in the airways prior to determining when to use BT”.

The Work Loss Data Institute’s guideline on “Asthma. In: Pulmonary (acute & chronic)” (2013) stated that “Bronchial thermoplasty, utilizes heat to decrease the smooth muscle mass/function in the larger bronchial airways. It is still to be considered an experimental approach until more data can be presented. It has been used in individuals with severe asthma who fail traditional, aggressive forms of therapy. These individuals may not always be identified clinically or by physiologic parameters”.

In a Cochrane review, Torrego et al (2014) examined the safety and effectiveness of BT in adults with bronchial asthma. These investigators searched the Cochrane Airways Group Specialized Register of Trials (CAGR) up to January 2014. They included RCTs that compared BT versus any active control in adults with moderate or severe persistent asthma. The primary outcomes were quality of life, asthma exacerbations and adverse events. Two review authors independently extracted data and assessed risk of bias. These researchers included 3 trials (429 participants) with differences regarding their design (2 trials compared BT versus medical management and the other compared BT versus a sham intervention) and participant characteristics; 1 of the studies included participants with more symptomatic asthma compared with the others. The pooled analysis showed improvement in quality of life at 12 months in participants who received BT that did not reach the threshold for clinical significance (3 trials, 429 participants; mean difference (MD) in Asthma Quality of Life Questionnaire (AQLQ) scores 0.28, 95 % confidence interval (CI) 0.07 to 0.50; moderate-quality evidence). Measures of
symptom control showed no significant differences (3 trials, 429 participants; MD in Asthma Control Questionnaire (ACQ) scores -0.15, 95 % CI: -0.40 to 0.10; moderate-quality evidence). The risk of bias for these outcomes was high because 2 of the studies did not have a sham intervention for the control group. The results from 2 trials showed a lower rate of exacerbation after 12 months of treatment for participants who underwent BT. The trial with sham intervention showed a significant reduction in the proportion of participants visiting the emergency department for respiratory symptoms, from 15.3 % on sham treatment to 8.4 % over 12 months following BT. The trials showed no significant improvement in pulmonary function parameters (with the exception of a greater increase in morning PEF in 1 trial). Treated participants who underwent BT had a greater risk of hospitalization for respiratory adverse events during the treatment period (3 trials, 429 participants; risk ratio 3.50, 95 % CI: 1.26 to 9.68; high-quality evidence), which represents an absolute increase from 2 % to 8 % (95 % CI: 3 % to 23 %) over the treatment period. This meant that 6 of 100 participants treated with BT (95 % CI: 1 to 21) would require an additional hospitalization over the treatment period. No significant difference in the risk of hospitalization was noted at the end of the treatment period. Bronchial thermoplasty was associated with an increase in respiratory adverse events, mainly during the treatment period. Most of these events were mild or moderate, appeared in the 24-hour post-treatment period, and were resolved within a week. The authors concluded that BT for patients with moderate to severe asthma provides a modest clinical benefit in quality of life and lower rates of asthma exacerbation, but no significant difference in asthma control scores. The quality of life findings were at risk of bias, as the main benefits were seen in the 2 studies that did not include a sham treatment arm. This procedure increases the risk of adverse events during treatment but has a reasonable safety profile after completion of the bronchoscopies. The overall quality of evidence regarding this procedure is moderate. For clinical practice, it would be advisable to collect data from patients systematically in independent clinical registries. Moreover, they stated that further research should provide better understanding of the mechanisms of action of BT, as well as its effect in different asthma phenotypes or in patients with worse lung function.

Kaukel et al (2014) stated that BT is a new treatment option for patients with severe bronchial asthma who remain symptomatic despite maximal medical therapy. The aim of this interventional therapy option is the reduction of smooth muscle in the central and peripheral airways in order to reduce symptomatic broncho-constriction via the application of heat. A full treatment with BT is divided into 3 bronchoscopies. Randomized, controlled clinical trials have shown an increase in quality of life, a reduction in severe exacerbations, and decreases in ED visits as well as days lost from school or work. The trials did not show a reduction in hyper-responsiveness or improvement in FEV1. Short-term adverse effects include an increase in exacerbation rate, an increase in respiratory infections and an increase in hospitalizations. In
the 5-year follow-up of the studies available there was evidence of clinical and functional stability of the treated patients. Moreover, the authors concluded that further studies are needed to identify an asthma phenotype that responds well to this treatment.

Iyer and Lim (2014) noted that BT involves the application of radiofrequency energy to visible proximal airways to selectively ablate airway smooth muscle. Bronchial thermoplasty is the first non-pharmacologic interventional therapy approved by the FDA for severe asthma. This approval was based on the results of the pivotal Asthma Intervention Research (AIR)-2 trial, which is the only randomized, double-blind, sham-controlled trial of BT. The primary end-point of the AIR-2 trial was improvement in the AQLQ. The results of the AIR-2 trial have generated enormous interest, controversy, and confusion regarding the true effectiveness of BT for severe asthma. Current marketing of BT highlights its use for patients with "severe" asthma, which is interpreted by most practicing clinicians as meaning oral corticosteroid dependence, frequent exacerbations, or a significantly reduced FEV1 with a poor quality of life. Did the AIR-2 trial include patients with a low FEV1, oral steroid dependence, or frequent exacerbations? Did the trial show efficacy for any of the primary or secondary end-points? The FDA approved the device based on the reduction in severe asthma exacerbations. However, were the rates of asthma exacerbations, ED visits, or hospitalizations truly different between the 2 groups, and was this type of analysis even justified given the original study design? This commentary was designed to specifically answer these questions and help the practicing clinician navigate the thermoplasty literature with confidence and clarity. The authors carefully dissected the design, conduct, and results of the AIR-2 trial and raised serious questions about the effectiveness of BT.

Bezzi et al (2014) stated that BT is a new modality for treating asthma. It targets ASM by delivering a controlled specific amount of thermal energy (radiofrequency ablation) to the airway wall through a dedicated catheter. The use of BT has been widely discussed for its potential in the treatment of asthma, since it seems to be able to reduce the symptoms of asthma. The definitive study for BT (AIR2 trial) employed a randomized, double-blind, sham-controlled design and enrolled 288 subjects with severe persistent asthma from 30 U.S. and international centers. The results of the AIR2 trial demonstrated clinically significant benefits of BT compared with the sham group at 1 year post-treatment, including an improvement in asthma-related quality of life, 32 % reduction in severe exacerbations, 84 % reduction in ED visits for asthma symptoms, and a 66 % reduction in time lost from work/school/other daily activities because of asthma symptoms. Pre-clinical work showed that ASM is reduced after BT by at least 3 years after treatment. The recent article from the AIR2 trial study group analyzed the long-term safety and effectiveness of BT in patients with severe persistent asthma and demonstrated the 5-year durability of the benefits of BT in the control of symptoms and safety. It supports the evidence that reduction in asthma attacks, ER visits, and hospitalizations for respiratory symptoms are maintained for at least 5 years. The authors concluded that there is a pressing need to understand the underlying
mechanism(s) of BT and how the delivered heat is translated into clinical benefit. This necessitates additional investigation to identify disease and patient characteristics that would enable accurate phenotyping of positive responders to avoid unnecessary procedures and risks.

Guidelines from the American Thoracic Society and the European Respiratory Society (Chung et al, 2014) stated that “we recommend that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board approved independent systematic registry, or a clinical study”. This is a strong recommendation, based upon very low quality of evidence.

Guidelines from the Global Initiative for Asthma (GINA, 2015) stated that “for highly selected adult patients with uncontrolled asthma despite use of recommended therapeutic regimens and referral to an asthma specialty center (Step 5), bronchial thermoplasty is a potential treatment option in some countries”. The guidelines stated that “evidence is limited and in selected patients” and that “the long-term effects are not known”. The guidelines stated that “caution should be used in selecting patients for this procedure, as the number of studies is small, and people with chronic sinus disease, frequent chest infections or FEV1 less than 60 percent predicted were excluded”. The guidelines also stated that “more studies are needed to identify its efficacy and long-term safety in broader severe asthma populations”. The guidelines explain that “carefully controlled trials are important as a large placebo effect has been seen in studies to date”. The guidelines explain: "In this bronchoscopic treatment, the airways are treated during three separate bronchoscopies with a radiofrequency pulse. The treatment is associated with a large placebo effect. In studies of patients taking high dose ICS/LABA, the treatment is associated with an increase in asthma exacerbations during the 3 month treatment period, and a subsequent decrease in exacerbations. There is no beneficial effect on lung function or asthma symptoms compared with sham-controlled patients. Extended follow up of some of the cohort confirmed a sustained reduction in exacerbations compared with pre-treatment. However, longer term follow up of larger cohorts comparing effectiveness and safety in both active and sham-treated patients is needed . . . The initial consensus recommendations byGINA about bronchial thermoplasty were based upon an assessment of evidence using the GRADE methodology, and were updated in 2014 following a review of later evidence. The 2014 European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force on Severe Asthma recommends that bronchial thermoplasty should be performed in adults only in the context of an independent Institutional Review Board-approved systematic registry or a clinical study, so further evidence about effectiveness and safety of the procedure can be accumulated."

Miller and Murgu (2014) stated that emphysema and asthma are responsible for economic and social burden. Altering the natural course of these diseases is a field of intense research. The National Emphysema Treatment Trial showed that lung volume reduction surgery (LVRS) could
significantly reduce both morbidity and mortality in properly selected patients. Lung volume reduction surgery is seldom performed, however, due to the high morbidity associated with the surgery. Numerous bronchoscopic interventions have been introduced with the goal of providing the clinical benefits of LVRS without the surgical complications. Thus far, these modalities have not produced the results once hoped. However, through active modification of both technique and patient selection, the role of minimally invasive modalities in the treatment of emphysema continues to evolve. Bronchial thermoplasty is a method of delivering controlled heat to airway mucosa with the goal of reducing airway smooth muscle mass and hence bronchoconstriction. In patients suffering from asthma who cannot achieve control with standard medical care, BT has been shown to be safe and improves symptoms, with long lasting benefit. Bronchial thermoplasty does not seem to affect traditional markers of asthma severity such as FEV1 and questions remain regarding proper patient selection for this therapy and its true physiologic effects.

Heinen et al (2014) noted that new treatments are needed to improve the care of severe asthmatic patients. Bronchial thermoplasty aims to lessen the airway smooth muscles via the heating of bronchial walls by radiofrequency. The preliminary studies showed a good tolerance and some good efficacy. Randomized controlled trials have been undertaken on moderate-to-severe asthmatic patients, demonstrating an improvement in quality of life, rate of severe exacerbations and unscheduled medical visits. The main side-effects consist of asthma exacerbations, atelectasis and infections. The authors concluded that BT is an innovative treatment with good efficacy and acceptable tolerance for moderate-to-severe asthmatic patients. Moreover, they stated that more studies are needed to better understand its mechanism of action and more clearly delineate the precise indications of this innovative technique.

Iyer and Lim (2015) stated that BT is the first non-pharmacologic interventional therapy approved by the FDA in 2010 for severe asthma. This approval was based on randomized sham-controlled trial called Asthma Intervention Research 2 (AIR2) published in 2010. Bronchial thermoplasty involves the application of radiofrequency energy to airways with an aim to selectively ablate airway smooth muscle; it is currently marketed for patients with "severe" asthma. Most practicing clinicians apply this severity category to patients with oral corticosteroid dependence, frequent exacerbations, or a significantly reduced FEV1 along with a poor quality of life. These researchers noted that there are unanswered questions regarding the AIR2 trial: Did the patients studied in the AIR-2 trial have these clinical features? Was there a reduction in severe asthma exacerbation achieved in the intervention group? Did any of the primary or secondary end-points in the AIR-2 trial show a positive signal? The authors stated that there continues to be controversy regarding patient selection and primary outcome; its effectiveness in the management of the patient with difficult-to-manage asthma is uncertain.
Kane et al (2015) stated that a small percentage of asthmatics have “severe refractory asthma”, where there is suboptimal response to currently available therapies. A number of novel therapies targeting key biological targets are becoming available. Asthma is a heterogeneous disease, and systematic evaluation of patients is important to target therapies to the underlying inflammatory subtype and clinical features. These investigators outlined new and emerging treatments for severe asthma, including monoclonal antibodies targeting eosinophilic disease, anti-neutrophil strategies, novel bronchodilators and BT.

Andrychiewicz et al (2015) noted that despite modern medicine’s greatest efforts, many patients suffering from COPD and asthma remain refractory to the best treatments available. Bronchoscopy is increasingly being used to explore new approaches for treating these diseases, and several new techniques have recently shown encouraging results. These researchers shed some light on these methods. They searched PubMed and Embase for English language articles from 1995 to September 2014, as well as ongoing trials on ClinicalTrials.gov. The following pre-specified terms were used to search for clinical trials and case reports from the past 20 years: “endoscopic treatment of COPD”, “endobronchial valve”, and “bronchial thermoplasty”. In search for new COPD treatments, several trials have assessed the effectiveness of 1-way valves and other conceptually similar techniques including biological sealants and thermal vapor ablation. These methods all operate within a similar paradigm where the intention is to maximize ventilation of the remaining healthy parts of the lung, and to minimize the use and the space occupied by the diseased lung tissue. Similarly, a new non-pharmacologic therapeutic approach in asthma, BT, was recently approved for use in the United States for adults with severe disease. The goal is to use to reduce the mass of hypertrophied smooth muscle in the bronchi to decrease bronchoconstriction. The authors concluded that both BT and the bronchoscopic treatments for COPD have shown promising results in recent studies, suggesting the onset of a new direction in obstructive lung disease treatment.

An UpToDate review on “Treatment of severe asthma in adolescents and adults” (Wenzel, 2015) states that “Bronchial thermoplasty (BT) refers to a technique of applying heat (via a device that delivers localized controlled radiofrequency waves) to the airways during bronchoscopy, which based on studies in dogs reduces the increased mass of airway smooth muscle associated with asthma. Due to the risk of the procedure and modest degree of improvement, additional data are needed regarding long-term effects and morphologic changes in the airways in order to determine the ideal role for BT in asthma. Thus, for patients who meet criteria for BT (i.e., require intermittent or continuous oral glucocorticoids, have a forced expiratory volume in one second [FEV1] ≥ 50% of predicted, have not had a life-threatening exacerbation in the past, and are willing to accept the risk of an asthma exacerbation requiring hospitalization as a consequence of the procedure), we advise undergoing BT in the context of a clinical trial or registry.”
An assessment by the BlueCross BlueShield Association Technology Evaluation Center concluded that bronchial thermoplasty did not meet TEC criteria: "The substantial response observed following a sham procedure in AIR2 emphasizes the necessity of a sham control to estimate treatment effects. Although a number of outcomes in the AIR2 trial favored BT, others did not, and for those that did effect magnitudes could be interpreted as modest. BT is accompanied by a risk of adverse events during the treatment phase that may require hospitalization—a tradeoff for potential future benefit. Although under conditions of controlled trials and careful patient selection, the morbidity from adverse events was not described as concerning, adoption outside those settings where patient selection may be less strict and providers less experienced with the device could be accompanied by a different adverse event profile. There is very little published evidence obtained outside the investigational setting on potential harms and benefit."

The Canadian Agency for Drugs and Technologies in Health’s assessment on “Bronchial thermoplasty for severe asthma” (2015) stated that “BT employs radiofrequency energy pulses to selectively reduce the thicker airway smooth muscle found in asthmatic patients. This selective ablation is thought to reduce airway hyper-responsiveness, airway obstruction, and asthma symptoms. Further research is required to help more clearly determine the mechanisms of action of bronchial thermoplasty. Limitations of the technique include the inability to treat distal symptomatic airways due to their small diameter, and contraindications for patients with implanted medical devices”. CADTH (2015) found: "Three randomized clinical trials, two that demonstrated evidence of performance bias, provided the evidence basis for the systematic review, two health technology assessments, two economic studies and four guidelines on bronchial thermoplasty identified and reviewed in this report. For patients with poorly controlled, severe asthma limited evidence suggested a marginal improvement in quality of life for some patients who received bronchial thermoplasty. One randomized controlled trial reported decreased emergency department visits following the bronchial thermoplasty treatment period as compared to a sham control. During the bronchial thermoplasty treatment period, consistent evidence was identified for an increased incidence of respiratory related adverse events requiring hospitalization in the treatment group. This increase did not extend past the treatment period or in five years of follow-up of treated patients. Other outcomes, including asthma control, respiratory related hospitalizations, frequency of severe exacerbations, and pulmonary function outcomes were either not improved or the evidence was mixed. One economic analysis found that when decreased emergency department visits and hospitalizations followed bronchial thermoplasty an increase in cost-effectiveness was realized, while another found that this decreased resource use may provide savings within five years when introduced into an asthmatic cohort of patients. No clear recommendations on which patient populations would
benefit most from bronchial thermoplasty were provided, however three of the four identified guidelines conditionally recommended bronchial thermoplasty as a potential treatment option for poorly controlled, severely asthmatic patients already on optimal pharmacological therapy.

Laxmanan and Hogarth (2015) stated that BT is a novel therapy for patients with severe asthma. Using radio frequency thermal energy, it aims to reduce the airway smooth muscle mass. Several clinical trials have demonstrated improvements in asthma-related quality of life and a reduction in the number of exacerbations following treatment with BT. In addition, recent data has demonstrated the long-term safety of the procedure as well as sustained improvements in rates of asthma exacerbations, reduction in health care utilization, and improved quality of life. The authors stated that further study is needed to elucidate the underlying mechanisms that result in these improvements. In addition, improved characterization of the asthma sub-phenotypes likely to exhibit the largest clinical benefit is a critical step in determining the precise role of BT in the management of severe asthma.

Chakir et al. (2015) evaluated the effects of BT on airway smooth muscle mass and airway collagen deposition in adult patients with asthma, regardless of pre-treatment smooth muscle area. A total of 17 patients with asthma underwent BT over the course of 3 visits. At Visit 1, bronchial biopsies were taken from the lower lobe that was not treated during this session. At Visit 2 (3 to 14 weeks after the first visit), all 17 patients underwent biopsy of the lower lobe treated during the first procedure. At Visit 3 (7 to 22 weeks after the first visit), 9 patients agreed to undergo biopsy of the same lower lobe. Histological and immunohistochemical analyses were performed on the biopsy specimens. Bronchial thermoplasty decreased airway smooth muscle from 12.9 ± 1.2 % of the total biopsy surface at Visit 1 to 4.6 ± 0.8 % at Visit 2 (p < 0.0001). For the 9 patients who underwent a third biopsy, mean airway smooth muscle area was 5.3 ± 1.3 % at Visit 3 (p = 0.0008 compared with baseline). Bronchial thermoplasty also decreased Type I collagen deposition underneath the basement membrane from 6.8 ± 0.3 μm at Visit 1 to 4.3 ± 0.2 μm at Visit 2 (p < 0.0001) and to 4.4 ± 0.4 μm for 9 patients at Visit 3 (p < 0.0001 compared with baseline). Over the course of 1 year after treatment, the doses of ICS, the number of severe exacerbations, and asthma control all improved (p ≤ 0.02). The authors concluded that for patients with severe asthma, BT reduced the smooth muscle mass of treated airway segments, regardless of the baseline level of muscle mass. Treatment also altered the deposition of collagen. At follow-up, BT improved asthma control; however, the limited number of subjects did not allow the authors to evaluate possible correlations between these improvements and the studied histological parameters. They stated that further studies are needed to confirm these results and evaluate their persistence.
Zhang et al (2016) evaluated the safety and effectiveness of BT in the treatment of severe asthma. The safety and effectiveness of BT were studied prospectively in 6 patients with poorly controlled severe asthma on long-term inhaled high-dose glucocorticoids and LABA. Outcomes assessed after BT included asthma symptoms, frequency of acute exacerbations, pulmonary function, medication adjustment, and post-operative complications at 6 and 12 months after treatment. The mini-AQLQ scores (6.4 ± 0.5), the frequency of acute exacerbations [0.4 (0.1 to 1.3) times/month], and the symptom-free days [(21.2 ± 7.2) days/month] were significantly improved at 6 months after operation compared to those before operation [5.2 ± 0.9, 2.0 (0.9 to 4.0) times/month, (14.5 ± 3.7) days/month, respectively, p < 0.05]. Data collected at the 6(th) month indicated significant improvements in the variation rate of PEF, the dose of inhaled glucocorticoids and oral glucocorticoids [(5.6 ± 3.3) % versus (21.1 ± 7.8) %), (800 ± 620) versus (1,133 ± 432) µg/day), 9.7 (1.3 to 10.0) versus 15.0 (10 to 20) mg/day, p < 0.05]. Outcomes mentioned above were improved as well at the 12(th) month. But the ACQ-6 scores, ACT scores, the ratio of PEF and its predicted value (%), the ratio of FVC and its predicted value (%), the ratio of FEV1 and its predicted value (%) were not changed significantly (p > 0.05). The PEF values and lung function measurements remained stable throughout the study period. The most common complications were cough (24.1 %), wheezing (13.8 %), followed by lower respiratory infection and atelectasis during the treatment. Pneumothorax and respiratory failure occurred in 1 patient 12 hours after the third procedure. The authors concluded that their preliminary study demonstrated promising effect of BT in the treatment of severe asthma, although there are some complications that need further observation.

Zafari et al (2016) noted that BT is a recently developed treatment for patients with moderate-to-severe asthma. A few studies have suggested the clinical effectiveness of this intervention. However, no study has evaluated the cost-effectiveness of BT compared to other alternative treatments for moderate-to-severe allergic asthma, which currently include omalizumab and standard therapy. These researchers evaluated the cost-effectiveness of standard therapy, BT, and omalizumab for moderate-to-severe allergic asthma in the USA. A probabilistic Markov model with weekly cycles was developed to reflect the course of asthma progression over a 5-year time horizon. The study population was adults with moderate-to-severe allergic asthma whose asthma remained uncontrolled despite using high-dose ICS, with or without LABA. A perspective of the health-care system was adopted with asthma-related costs as well as quality-adjusted life years (QALYs) and exacerbations as the outcomes. For standard therapy, BT, and omalizumab, the discounted 5-year costs and QALYs were $15,400 and 3.08, $28,100 and 3.24, and $117,000 and 3.26, respectively. The incremental cost-effectiveness ratio (ICER) of BT versus standard therapy and omalizumab versus BT was $78,700/QALY and $3.86 million/QALY, respectively. At the willingness-to-pay (WTP) of $50,000/QALY and $100,000/QALY, the probability of BT being cost-effective was 9 %, and 67 %, respectively. The corresponding expected value of perfect information (EVPI) was $155 and $1,530 per individual at these
thresholds. In sensitivity analyses, increasing the costs of BT from $14,900 to $30,000 increased its ICER relative to standard therapy to $178,000/QALY, and decreased the ICER of omalizumab relative to BT to $3.06 million/QALY. Reducing the costs of omalizumab by 25 % decreased its ICER relative to BT by 29 %. The authors concluded that based on the available evidence, the findings of this study suggested that there is more than 60 % chance that BT becomes cost-effective relative to omalizumab and standard therapy at the WTP of $100,000/QALY in patients with moderate-to-severe allergic asthma. However, they stated that there is a substantial uncertainty in the underlying evidence, indicating the need for future research towards reducing such uncertainty.

Laxmanan et al (2016) stated that BT is a therapeutic intervention for patients with severe persistent asthma that delivers targeted thermal energy to the airway walls with the goal of ablating the smooth muscle. Since the publication of the original pre-clinical studies, 3 large randomized clinical trials evaluating its impact on asthma control have been performed. These trials have shown improvements in asthma related quality of life and a reduction in asthma exacerbations following treatment with BT. However, there remains significant controversy regarding the true effectiveness of BT and the interpretation of these studies, particularly the AIR2 Trial -- no meaningful differences were noted between the BT group and the control group in mean respiratory parameters, total symptom score, symptom-free days, rescue medication use, unscheduled physician visits, hospitalizations, or the ACQ scores at 1 year follow-up. An additional year of uncontrolled follow-up of the BT group evaluated with traditional statistical tools showed no statistically significant differences within this group between 1 year and 2 years follow-up in severe exacerbations, asthma symptoms, ED visits or hospitalizations follow-up.

An assessment by the National Institute for Health and Care Excellence (NICE, 2016) found that evidence from 3 systematic reviews (reporting on 3 randomized controlled trials of mixed quality) suggests that use of the Alair system is associated with some patient benefits (such as improved quality of life, and morning peak expiratory flow), but not all benefits were considered to be clinically significant. The assessment state that there is mixed evidence in relation to other outcomes (including asthma exacerbations, hospitalizations and emergency department visits).

An assessment by Hayes, Inc. for the Washington State Healthcare Authority (Hayes, 2016) concluded: "The overall body of evidence concerning thermoplasty for treatment of asthma was small in size and low in quality. The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series. The evidence for the effectiveness of bronchial thermoplasty for treating asthma was considered to be of low quality because of some positive but inconsistent results regarding short-term
benefits of bronchial thermoplasty, varied patient selection criteria across studies, small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long-term efficacy of bronchial thermoplasty."

Burn and co-workers (2017) noted that BT is a novel treatment for severe asthma. Its mode of action and ideal target patient group remain poorly defined, although clinical trials provided some evidence on safety and effectiveness. These researchers presented procedural and short-term safety evidence from routine United Kingdom (UK) clinical practice. Patient characteristics and safety outcomes (procedural complications, 30-day re-admission and accident and emergency (A&E) attendance, length of stay) were assessed using 2 independent data sources, the British Thoracic Society UK Difficult Asthma Registry (DAR) and Hospital Episodes Statistics (HES) database. A matched cohort (with records in both) was used to estimate safety outcome event rates and compare them with clinical trials. Between June 2011 and January 2015, a total of 215 procedure records (83 patients; 68 treated in England) were available from DAR and 203 (85 patients) from HES; 152 procedures matched (59 patients; 6 centers), and of these, 11.2 % reported a procedural complication, 11.8 % resulted in emergency respiratory re-admission, 0.7 % in respiratory A&E attendance within 30 days (20.4 % had at least 1 event) and 46.1 % involved a post-procedure stay. Compared with published clinical trials that found lower hospitalization rates, BT patients in routine clinical practice were, on average, older, had worse baseline lung function and asthma quality of life (QOL). The authors concluded that higher proportion of patients experienced AEs compared with clinical trials. The greater severity of disease among patients treated in clinical practice may explain the observed rate of post-procedural stay and re-admission. They stated that study of long-term safety and effectiveness requires continuing data collection.

Krmisky and associates (2017) stated that BT is a novel technique used in the treatment of severe asthma. Several randomized clinical trials demonstrated improvement in QOL and reduction in exacerbation rates after treatment. The authors concluded that further studies are needed in order to better describe the mechanism of action and the asthma sub-phenotype that would best benefit from this treatment, with particular attention on the effect of intervention in patients with most severe disease.

In a review on “Development of new therapies for severe asthma”, Fajt and Wenzel (2017) stated that although BT has emerged as a therapy for severe asthma, little is understood regarding the appropriate selection of these patients.

Debray and colleagues (2017) stated that BT is a recent, promising and well-tolerated technique for the treatment of severe asthma. By delivering thermal energy to the airway wall, this procedure can induce early pulmonary opacities seen on computed tomography (CT). These
researchers examined early CT modifications induced by BT and determined their association with respiratory symptoms. Unenhanced chest CT was performed the day after each BT session in 13 patients with severe asthma, leading to the examination of 38 treated lobes. A total of 15 BT-treated lobes were evaluated in 11 patients at 1 month. The 1st 2 patients also underwent CT at 1 week. No symptoms suggestive of pulmonary infection were noted following BT in any patient. Peri-bronchial consolidations and ground-glass opacities were observed in all treated lobes on day 1, with 3 lower lobes showing complete collapse. Mild involvement of an adjacent untreated lobe was observed in 12 out of 38 (32 %) cases. Opacities had decreased in 5 out of 15 (33 %) and disappeared in 10 out of 15 (67 %) at 1 month. The authors concluded that BT induced early pulmonary peri-bronchial hyper-densities in all treated lobes; these alterations were unrelated to clinical symptoms and spontaneously decreased or disappeared after 1 month.

Oberle and Mathur (2017) noted that the inflammatory make-up of severe asthma is heterogeneous. Identification of the predominant cellular endotype via biomarkers can aid in the selection of more advanced therapies. This review was clinically focused on how to use these biomarkers to help select between biologic agents and/or BT. Several Th2 biomarkers exist for the detection of eosinophilic disease; however, the best biomarker for clinical practice is debatable depending upon local resources. Currently, there are 3 federal drug agency-approved biologic agents (omalizumab, mepolizumab and reslizumab) to treat severe asthma with frequent exacerbations despite standard medical therapy. Several others are either in clinical trials or in the development phase for the treatment of eosinophilic asthma. To-date, agents targeting neutrophilic inflammation have been largely unsuccessful; BT has emerged as an option for the treatment of severe asthma. The authors concluded that appropriate selection of patients through the use of eosinophilic biomarkers has led to significant reductions in exacerbations with the use of mAb therapy. They stated that BT has also shown reductions in asthma exacerbations and improved QOL; however, it is unclear which patients may respond best to this intervention.

Langton and colleagues (2017) stated that BT is an emerging bronchoscopic therapy for severe asthma. The predictive factors for clinical response to BT are unknown. These investigators examined the relationship between the number of radiofrequency (RF) activations applied and the treatment response observed. Data were collected from 24 consecutive cases treated at 3 Australian centers from June 2014 to March 2016. The baseline characteristics were collated along with the activations delivered. The primary response measure was change in the ACQ-5 score measured at 6 months post-BT. The relationship between change in outcome parameters and the number of activations delivered was explored. All patients met the ERS/ATS definition for severe asthma. At 6 months post-treatment, mean ACQ-5 improved from 3.3 ± 1.1 to 1.5 ± 1.1, p < 0.001. The minimal clinically significant improvement in ACQ-5 of greater than or equal to 0.5 was observed in 21 out of 24 patients. The only significant variable that differed between
the 21 responders and the 3 non-responders was the number of activations delivered, with 139 ± 11 activations in the non-responders, compared to 221 ± 45 activations in the responders (p < 0.01). A significant inverse correlation was found between change in ACQ-5 score and the number of activations, r = -0.43 (p < 0.05). These researchers noted that the findings of this study demonstrated that there was no loss of safety in performing BT with the catheter more peripherally advanced, and that the outcomes may be superior. However, this was a small study, and only 18% of the variation in change in ACQ-5 post-treatment was explained by variation in the number of activations applied. Thus, there may be other factors, not yet identified that predict patient response to BT. This highlights the need for a future multi-variate regression analysis of predictors of response to BT in a large cohort of patients. When completed, the Bronchial Thermoplasty Global Registry may provide an ideal opportunity to undertake this analysis and further examine the role of RF activations. The authors stated that this study demonstrated that there can be procedural differences between physicians in the application of RF treatment during BT, and that the resulting difference in activations can significantly affect patient outcomes.

Nguyen and associates (2017) developed a Markov model to estimate the costs and quality-adjusted life years (QALYs) gained with BT combined with optimized asthma therapy (BT-OAT) versus OAT from the societal and health system perspectives. The model was populated using Singapore-specific costs and transition probabilities and utilities from the literature. Sensitivity analyses were conducted to identify the main factors determining cost-effectiveness of BT-OAT. BT-OAT was not cost-effective relative to OAT over a 5-year time horizon with an incremental cost-effectiveness ratio (ICER) of $US138,889 per QALY from the societal perspective and $US139,041 per QALY from the health system perspective. The cost-effectiveness of BT-OAT largely depended on a combination of the cost of the BT procedure and the cost of asthma-related hospitalizations and ED visits. The authors concluded that based on established thresholds for cost-effectiveness, BT-OAT is not cost-effective compared with OAT in Singapore. Given its current clinical efficacy, BT-OAT is most likely to be cost-effective in a setting where the cost of BT procedure is low and costs of hospitalization and ED visits are high.

Furthermore, the Japanese Society of Allergology’s “Guidelines for Adult asthma” (Ichinose et al, 2017) states that “Bronchial thermoplasty has recently been developed for severe, persistent asthma, but its long-term efficacy is not known”.

In summary, although available data are promising, more research is needed to ascertain what role, if any, BT should play in the treatment of patients with asthma. Furthermore, there is a lack of evidence regarding the effectiveness of BT in the management of patients with chronic obstructive pulmonary disease.
Chupp and colleagues (2017) stated that BT is an endoscopic therapy for severe asthma. The previously reported, randomized sham-controlled AIR2 (Asthma Intervention Research 2) trial showed a significant reduction in severe asthma exacerbations, ED visits and hospitalizations after BT. These investigators compared outcomes in BT subjects with 3 years of follow-up from the ongoing, post-market PAS2 (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma) study with those from the AIR2 trial. A total of 279 subjects were treated with BT in the PAS2 study. These investigators compared the first 190 PAS2 subjects with the 190 BT-treated subjects in the AIR2 trial at 3 years of follow-up. The PAS2 subjects were older (mean age of 45.9 versus 40.7 years) and more obese (mean body mass index [BMI] of 32.5 versus 29.3 kg·m⁻²) and took higher doses of inhaled corticosteroids (mean dose of 2,301 versus 1,961 μg·day⁻¹). More PAS2 subjects had experienced severe exacerbations (74 % versus 52 %) and hospitalizations (15.3 % versus 4.2 %) in the 12 months prior to BT. At year 3 after BT, the percentage of PAS2 subjects with severe exacerbations, ED visits and hospitalizations significantly decreased by 45 %, 55 % and 40 %, respectively, echoing the AIR2 results. The authors concluded that although the prospectively enrolled PAS2 study population in this article was described as “real-world”, the study eligibility criteria meant that the most severe subjects often seen in clinical practice were not included. Nevertheless, the 3-year results from this subset of subjects in the PAS2 study inspired confidence, because they suggested that the “real-world” results obtained after BT in the PAS2 study echoed those observed in the AIR2 RCT.

The authors noted that this study had several drawbacks: (i) geographical differences in the locations of the investigational sites varied between the PAS2 study, which included subjects from North America only, and the AIR2 trial, which was more global and included patients from North America, Europe, Brazil and Australia. These geographic differences might have had an impact on the subject characteristics and comorbidities seen in each study, (ii) as the PAS2 subjects were being followed for 5 years after BT, this study contained data on only a subgroup of subjects included in the study who have completed 3 years of follow-up. Additional analysis of the entire cohort at 3 and 5 years may further validate these observations, thus far consistent with the results of the AIR2 RCT. The analysis was further limited by differences between the PAS2 study and AIR2 trial. Due to its follow-up schedule, the PAS2 study collected AQLQ data only at baseline and not at the post-procedure follow-up visits due to concerns over the ability of this tool to reliably capture asthma-related QOL when only collected once-annually. Therefore, these researchers were unable to include this measure in their analysis. Also, the PAS2 study and AIR2 trial used slightly different definitions of severe asthma exacerbations, although a post-hoc evaluation for these definition differences showed a difference of only 1 severe exacerbation. Moreover, the indirect comparison between the randomized AIR2 trial and the single-arm PAS2 study may
be limited by cross-trial differences these researchers failed to identify in their analysis, and (iii) further subgroup analysis was needed to help identify which asthma subjects were most likely to benefit from the BT procedure in the “real-world”. This would benefit asthma subjects currently not well-managed with optimized pharmacological therapeutic options.

Blaiss and associates (2017) noted that severe asthma poses significant disease-related and economic burdens in the United States. Challenges in practice include how to define “severe asthma” for a given patient, knowing which are the right tests to perform and when, and having a better understanding of a patient's asthma phenotype. Furthermore, current guidelines do not address a clear, practical approach to treatment that is based on a patient's asthma phenotype. These investigators developed a consensus on the definition of severe asthma, the role of biomarkers and phenotyping severe asthma, and the use of newer biologic therapies and BT to help guide practicing clinicians. A roundtable meeting was convened with a panel of severe asthma experts to discuss areas in practice that are not adequately addressed by current guidelines, specifically phenotype-guided treatment. They described a consensus on the definition of severe asthma, asthma phenotyping with the use of available biomarkers, and guiding principles for newer biologic therapies and BT. The authors concluded that to optimize therapy and improve outcomes such as daily symptoms, QOL, exacerbations, and hospitalizations, a clear picture of a patient's asthma phenotype is needed to guide therapy. Determining asthma phenotypes is the foundation of precision medicine for this persistent, often difficult-to-treat disease. The panel stated that for non-allergic, non-eosinophilic (non-TH2) severe asthma, BT can be a first option for patients with persistent symptoms and who have variable airflow obstruction as demonstrated by bronchodilator reversibility after failure of triple therapy with high-dose ICS plus LABA and tiotropium, but before regular OCS use or a targeted biologic. Moreover, they stated that BT can also be considered an alternative therapy for patients with allergic or eosinophilic asthma who have had an inadequate response to initial biologic therapy. Moreover, it should be noted that the authors stated that participants of this panel acknowledged that the body of evidence needed to develop strong guidelines for the use of newer biologic therapies or BT is limited.

Niven and co-workers (2017) stated that BT as an add-on therapy for uncontrolled severe asthma is an alternative to biologic therapies like omalizumab (OM). These researchers conducted an indirect treatment comparison (ITC) to appraise comparative effectiveness of BT and OM. A systematic literature review identified relevant RCTs. The ITC followed accepted methodology, and it comprised a sham-controlled trial of BT (AIR2) and 2 placebo-controlled trials of OM (INNOVATE; EXTRA). Comparing the BT post-treatment period to ongoing treatment with OM, showed no significant differences in the rate ratios (RRs) for severe exacerbations (RR of BT versus OM = 0.91 [95% CI: 0.64 to 1.30]; p = 0.62) or hospitalizations
(RR = 0.57 [95% CI: 0.17 to 1.86]; p = 0.53); ED visits were significantly reduced by 75% with BT (RR = 0.25 [95% CI: 0.07 to 0.91]; p = 0.04); the proportions of patients with clinically meaningful response on the asthma QOL questionnaire were comparable (RR = 1.06 [95% CI: 0.86 to 1.34]; p = 0.59). The RR for exacerbations statistically favored OM over the total study period in AIR2 (RR = 1.50 [95% CI: 1.11 to 2.02]; p = 0.009) likely reflecting a transient increase in events during the BT peri-treatment period. The authors concluded that the ITC should be interpreted cautiously considering the differences between patient populations in the included trials. However, based on the analysis, BT compared well with a potentially more costly pharmacotherapy for asthma. Clinicians evaluating the relative merits of using these treatments should consider the totality of evidence and patient preferences to make an informed decision. Moreover, the authors noted that while it must be acknowledged that the findings of this ITC were best considered indicative rather than definitive, in the absence of RCT evidence that directly compared BT and OM or that allowed an indirect or mix treatment comparison in more comparable severe asthma populations, it provided the best available quantitative assessment of the relative efficacy of these 2 therapies. It should also be noted that this was an industry-sponsored study.

Chipps and colleagues (2017) stated that current asthma guidelines recommend a control-based approach to management that involves assessment of impairment and risk followed by implementation of treatment strategies individualized according to the patient's needs and preferences. The fact that many patients still experience severe symptoms that negatively affect QOL suggests that asthma control remains an objective to be achieved. Tools are available to help patients (and families) manage the day-to-day and short-term variability in asthma symptoms; however, when and how to implement a sustained step-up in therapy is less clear. The Asthma Yardstick is a comprehensive update on how to conduct a sustained step-up in asthma therapy for the patient with not well-controlled or poorly controlled asthma. Patient profiles and step-up strategies were based on current guidelines, newer data, and the authors' combined clinical experience and were intended to provide a practical and clinically meaningful guide toward the goal of well-controlled asthma for every patient. The development of this tool came in response to the continued need to proactively address the sustained loss of asthma control at all levels of severity. The authors noted that patients undergoing BT have better outcomes if at baseline there is greater ASM mass. There is no airway fibrosis after BT, and the procedure is safe, although a transient increase in AEs (including severe exacerbations) were observed immediately after the procedure compared with controls who underwent sham bronchoscopy. A small study of 42 patients undergoing BT suggested that a shorter duration of asthma and increased exacerbation rate might be predictors of BT response. Other factors that might be predictive included higher baseline oral corticosteroid (OCS) dose, lower QOL scores,
and older age. They stated that more research is needed to better identify patient characteristics or a specific phenotype that is more likely to benefit; most asthma guidelines recommend additional clinical trials.

On behalf of the Agency for Healthcare Research and Quality, D'Anci and colleagues (2017) evaluated the safety and effectiveness of BT in adults with asthma. These researchers systematically searched the gray literature and five bibliographic databases, Medline, Embase, PubMed, CINAHL, and the Cochrane Library, through April 20, 2017. Eligible studies included systematic reviews, meta-analyses, RCTs, and non-randomized interventional studies with concurrent controls. Case reports and series were also considered for describing AEs. Studies were evaluated for risk of bias using the Cochrane Risk of Bias instrument, and the evidence base was assessed using the methods guidance established by the Evidence-based Practice Center program. A total of 15 studies, including 3 RCTs with 5-year single-arm follow-up in BT-treated patients (n = 432 for the RCTs), examined the impact of BT in addition to standard care (continued medical management) on patients with asthma. BT and standard care improved asthma control (defined by the Asthma Control Questionnaire [ACQ] change from baseline to 12 months) and Asthma Quality of Life Questionnaire (AQLQ) scores more than standard care alone to a degree that was statistically significant but not clinically important (low strength of evidence [SOE]). However, BT and standard care, compared with a sham bronchoscopic procedure and standard care, did not improve asthma control (defined as ACQ change from baseline to 12 months), hospitalizations for respiratory symptoms, use of rescue medications, pulmonary physiology measures, or AQLQ scores (in the intention-to-treat analysis) (low SOE). In the same sham-controlled trial, BT reduced severe exacerbations after the 12-week treatment period to a statistically but not clinically important degree (low SOE), and patients undergoing BT had fewer ED visits than patients who had the sham bronchoscopic procedure (moderate SOE). In the RCTs comparing BT and standard care to standard care alone, evidence was insufficient to assess if BT reduced rates of severe exacerbations. Common AEs following BT during the 12-week treatment period in the RCTs included bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing. Hospitalizations were more common in patients undergoing BT than with either standard care alone or sham bronchoscopy during the 12-week treatment period, as were upper respiratory tract infections, wheezing, dyspnea, lower respiratory tract infections, anxiety, and segmental atelectasis, but the events were too infrequent to achieve statistical significance. Severe AEs (including post-procedure segmental atelectasis due to mucus plugging, hemoptysis, chest infections requiring hospitalization, and bronchial artery pseudo-aneurysm) were also reported in 6 case reports and 2 small case series. Following the 12-week treatment period, rates of respiratory-related hospitalizations were not significantly different between groups for up to 5 years of follow-up. No deaths were attributed to BT. The authors concluded that while asthma control and QOL measures modestly improved in patients undergoing BT compared to medical management
alone in 2 controlled but non-blinded studies, these measures did not improve in the sham-controlled study. The sham-controlled, blinded study found modest improvements in severe exacerbations and significantly fewer ED visits following BT compared to the sham bronchoscopic procedure, but serious AEs and post-procedure hospitalizations were more common during the 12-week treatment period in patients undergoing BT than in patients undergoing sham treatment. They stated that the available body of literature on BT was small and uncertainty remained about appropriate patient selection criteria and the effects of the treatment beyond 5 years.

Boulet (2018) stated that the term “airway remodeling” reflects changes in the type, quantity, and nature of airway wall components and their organization. The author reviewed recent publications on airway remodeling in asthma. Animal models and in-vitro studies have confirmed the involvement of airway epithelium, ASM, and extracellular matrix components in asthma-related airway remodeling. They reported influences on proliferation of ASM cells, and how their orientation or morphology, in addition to the heterogeneity of ASM mass at different levels of airways could influence their effects. Clinical benefits have been observed following reduction of ASM following BT. Asthmatic epithelial cell transcriptome alterations were found to involve metabolism and epigenetics, beyond epithelial mesenchymal trophic unit driven by injury and repair in chronic inflammation. New ways to explore airway remodeling such as imaging or endoscopic techniques have been evaluated. Finally, new data support the role of eosinophils and mast cells in remodeling and show the influence of new asthma drugs on this process. The authors concluded that “as recently stated by an American Thoracic Society task force, we need more research on airway remodeling, its determinants and clinical relevance, and on the effects of asthma drugs on its various components”.

Minami and colleagues (2018) noted that BT is a novel procedure for patients with severe asthma showing a stable lung function. These investigators reported 2 cases with a deteriorating lung function. The lung function tended to improve in one case, while the other case discontinued mepolizumab medication after the procedure. Treatment was performed safely under general anesthesia in both cases. The authors concluded that the use of BT may therefore be useful for the treatment of patients with a deteriorating lung function. Moreover, they stated that prospective studies are needed to improve the levels of safety and patient satisfaction associated with this procedure.

Thomson (2018) stated that BT is a licensed non-pharmacological treatment for severe asthma. The author evaluated evidence for the safety and efficacy of BT from clinical trials and observational studies in clinical practice, and reviewed its place in the management of severe asthma, predictors of response and mechanisms of action. The author concluded that BT improves QOL and reduces exacerbations in moderate-to-severe asthma. Morbidity from
asthma is increased during treatment. Overall, patients treated in clinical practice have worse baseline characteristics and comparable clinical outcomes to trial data. Follow-up studies provided reassurance on long-term safety. The author stated that despite some progress, future research needs to investigate uncertainties about predictors of response, mechanism of action and place in management of asthma.

An UpToDate review on “Treatment of severe asthma in adolescents and adults” (Wenzel, 2018) states that “Bronchial thermoplasty involves targeted application of heat (via radiofrequency waves) to the airways and is approved for use in selected adults with severe asthma that is not well-controlled with inhaled glucocorticoids and long-acting beta agonists. Due to the risk of the procedure and modest degree of improvement, additional data are needed to determine the ideal role for BT in asthma. Thus, we advise patients who meet criteria for BT and are willing to accept the risk of an asthma exacerbation requiring hospitalization to participate in a clinical trial or registry”.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>31660</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed;</td>
</tr>
<tr>
<td></td>
<td>with bronchial thermoplasty, 1 lobe</td>
</tr>
<tr>
<td>31661</td>
<td>2 or more lobes</td>
</tr>
<tr>
<td>J41.0 - J47.9</td>
<td>Chronic lower respiratory diseases and hypersensitivity pneumonitis due to organic dust [including asthma]</td>
</tr>
<tr>
<td>J67.0 - J67.9</td>
<td>Chronic lower respiratory diseases and hypersensitivity pneumonitis due to organic dust [including asthma]</td>
</tr>
</tbody>
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The above policy is based on the following references:


27. Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of asthma. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); June 2010.
36. Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of chronic obstructive pulmonary disease (COPD). Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); March 2011.


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There are no amendments for Medicaid.

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